Total Synthesis of Optically Active Plagiospirolides A and B: Highly Stereoselective Biomimetic Diels–Alder Reaction*

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Based on biogenetic hypothesis, optically active plagiospirolides A and B (C_{35}-terpenoids) have been synthesized by a Diels–Alder reaction between independently synthesized sesquiterpenoids (diplophyllolide A and diplophyllin) and a 5–8–5-membered tricyclic diterpenic hydrocarbon prepared from a $CrCl_2$-mediated condensate of (3*S*)-benzyloxyirid-1-en-7-al and (3*R*)-7-chloroirid-1-ene.

Among the natural products, there are many compounds which are regarded as being formed *via* cycloaddition processes *in vivo*. The structures of plagiospirolides A (**1**) and B (**2**), isolated from the liverwort *Plagiochila moritziana*,[2] represent unique members of this class of biochemical Diels–Alder products, suggested to be biosynthesized from eudesmanolide sesquiterpenoids and a fusicoccane diterpenic hydrocarbon in a formal sense. Later, the congeners plagiospirolides C and D, having the same carbon skeleton as compounds **1** and **2**, and plagiospirolide E, a Dields–Alder adduct of two sesquiterpenoids, were characterized (Fig. 1).[3]

At the present time, there are many apparent Diels–Alder adducts derived from two different precursors; *i.e.*, ornativolides **A** from *Geigeria ornativa*,[4] pungiolides **B** from *Xanthium pungens*,[5] shizukaol **A C** from *Chloranthus japonicus*,[6] biennin **C D** from *Hymenoxys biennis*,[7] methyl sarcophytoate **E** from *Sarcophyton glaucum*,[8] and aestivalin **F** from *Gaillardia aestivalis* (Fig. 2).[9] However, it is true that the reproduction of the biological process *in vitro* sometimes requires quite severe conditions.

For example, 'bissesquiterpenelactones' **G** and **H** isolated from *Helenium autumnale*,[10] which were thought to be biosynthesized from α-zingiberene **J**[11] and isoalantolactone **K**[12] and alantolactone **L**,[13] were not formed upon mixing of the components; in order to obtain 3% of the adducts, it was required to heat the mixture at 190 °C in chloroform for 2 h;[10] these can hardly be regarded as physiological conditions (Scheme 1).

Therefore, it was interesting to investigate the biogenetic Diels–Alder reaction leading to the total synthesis of compounds **1** and **2** *in vitro*. These superficial C_{35}-terpenoids can be considered as adducts of a 5–8–5-membered tricyclic diterpene **3** and sesquiterpenoids, diplophyllolide **A 4** and diplophyllin **5**, which have been isolated from *Diplophyllum albicans*.[14,15] The retrosynthesis of compounds **1** and **2** is shown in Scheme 2.

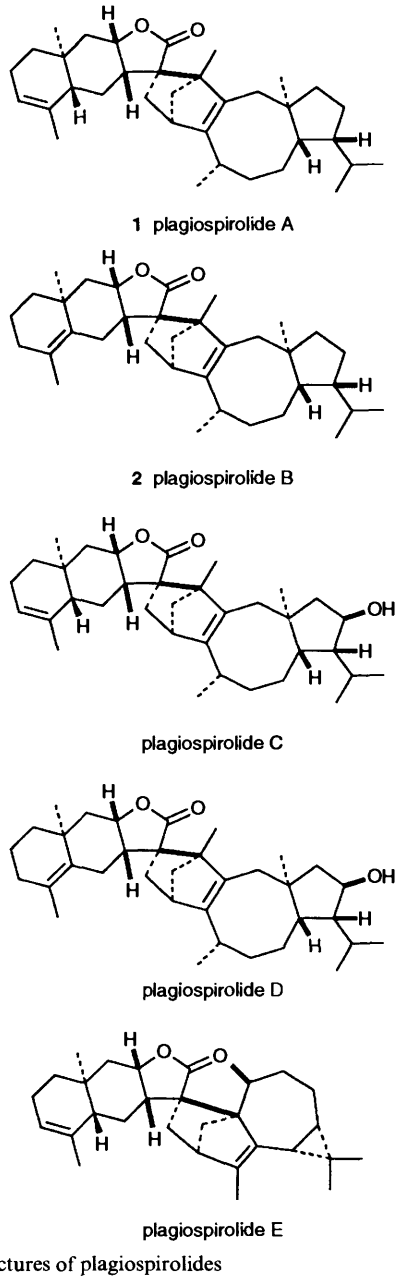


Fig. 1 Structures of plagiospirolides

Results and Discussion

In order to synthesize the diterpene component **3**, the optically active (3*S*,8*R*)-9-benzyloxyirid-1-en-7-al **6** and (3*R*)-7-chloroirid-1-ene **7**[16,17] were condensed with chromium(II) chloride in a mixed solution of *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) (2:1) with added propan-2-ol to obtain a condensate **8**[18] and its accompanying epimer **9** in 90 and 6% yield (Scheme 3); addition of propan-2-ol is essential to minimize the amount of by-product **9**. Hydroboration of compound **8** with thexylborane ($Me_2CHCMe_2BH_2$) stereospecifically afforded an alcohol **10**, whose hydrogenolysis with palladium-on-carbon afforded a triol **11** and a cyclized ether

† A preliminary account of this paper was reported (ref. 1).

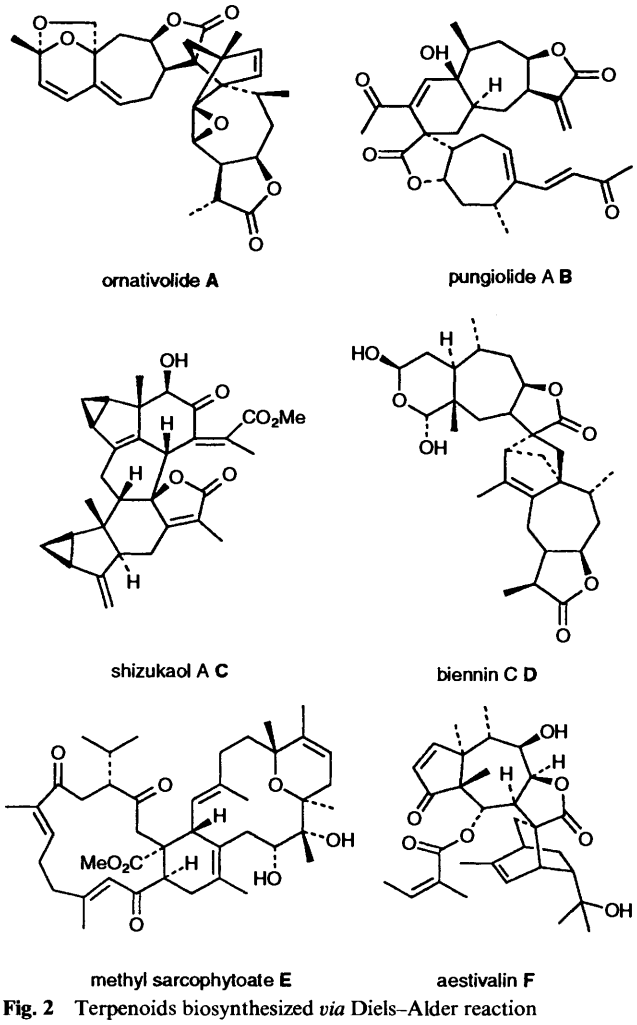
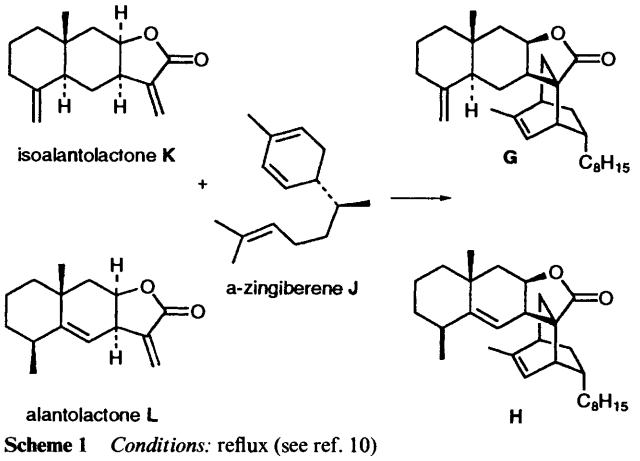


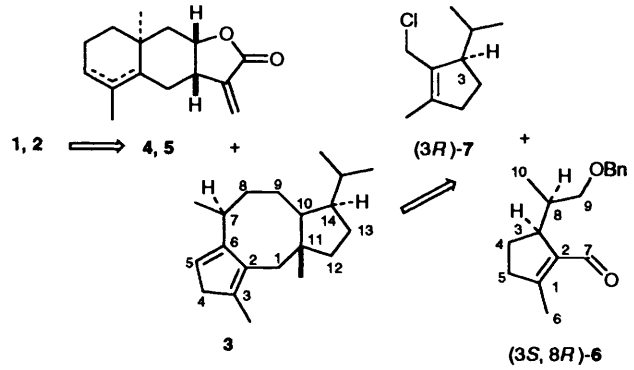
Fig. 2 Terpenoids biosynthesized *via* Diels–Alder reaction



Scheme 1 *Conditions:* reflux (see ref. 10)

derivative **12**. Treatment of triol **11** with mineral acid in THF afforded the ether **12**, which was, *via* Birch reduction, further converted into a diol **13**.

Swern oxidation of diol **13** gave a dialdehyde **14**. Subsequent titanium(II) chloride treatment[16,19] of dial **14** in a mixed solution of benzene and THF (5:1) gave the desired *cis*-glycols **15** and **16** in 37 and 9% yield, respectively. The same treatment of dial **14** in THF, a more polar medium, was unsatisfactory due to the occurrence of an aldol-type cyclization to a seven-membered derivative **17**.* Stereochemistries of *cis*-glycols **15** and **16** were differentiated by the observed nuclear Overhauser



Scheme 2

enhancement (NOE) in the ^{1}H NMR spectrum of compound **15** between the C-11 methyl group and 8-H and 9-H (10 and 3.5%, respectively), and that in compound **16** between the C-11 methyl and the hydroxy-group proton on C-9 (15%).

Eastwood–Ando reductive elimination[20,21] of the orthoformates **18a** and **18b** from glycols **15** and **16**, respectively, gave the same diene **19**, whose catalytic reduction gave dihydro derivatives **20** and **21** (5:3) in quantitative yield (Scheme 4). Oxidation of this mixture with singlet oxygen ($^1O_2$) generated by means of Rose Bengal-photosensitization, followed by reduction with triphenylphosphine and dehydration with silica gel, afforded a mixture of cyclopentadienes **3** and **22** (3:2)† in 91% yield. Treatment of the mixture with butyllithium afforded a cyclopentadienide **23**, which upon protonation with *tert*-butyl alcohol formed a single isomer **3**, which gave the above mentioned equilibrated mixture, **3**:**22** = 3:2, by heating at 80 °C.

Meanwhile, the other components, optically active isomeric tricyclic lactones **4** and **5**, were prepared[22] *via* a rather conventional route with a modification of Caine's synthesis of racemic 3-oxodiplophyllin (Scheme 5).[23]

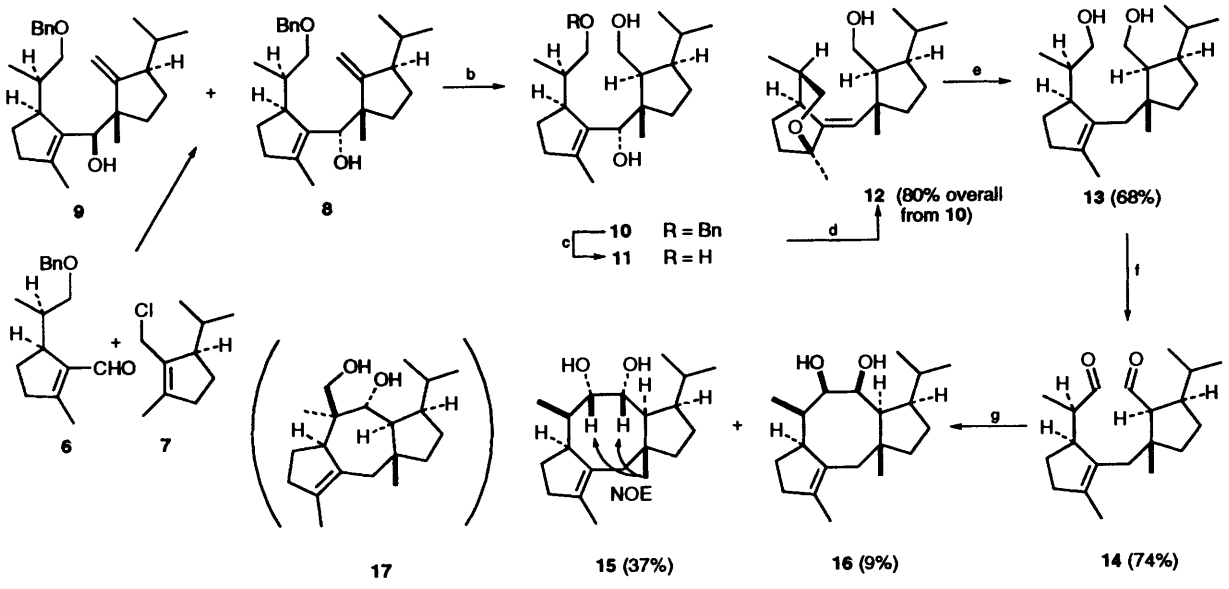
Diels–Alder reaction of diplophyllin **5** with a mixture of diterpenes **3** and **22** was carried out in [$^2H_6$]benzene and the reaction was monitored by ^{1}H NMR spectroscopy. After confirmation of the appearance of new signals ascribable to a Diels–Alder adduct, at 25 °C, the mixture was heated at 40–60 °C for 40 h to facilitate the reaction. It should be mentioned that the natural product **2** is one of eight possible Diels–Alder adducts from substrates **3** and **5**. Besides a minor product, whose presence was detected on TLC but whose structure has not yet been determined, only one compound could be isolated, which was indeed compound **2**, an oil, $[\alpha]_{436}^{21}$ +130‡ (*c* 0.10) (lit.,[2] +135.1). This result suggests that dienes **22** and **3** thermally equilibrated under the reaction conditions, and that isomer **22** is less reactive than isomer **3**. The ^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectra of the product **2** were consistent with the reported data. The specific optical-rotation values of the samples, from both origins, synthetic and natural, of compound **2** were the same within experimental error. Since our starting materials are optically pure without ambiguity in the absolute configuration, this derivation to compound **2** has clarified its absolute configuration as that depicted.

Again, the Diels–Alder reaction of compound **4** and the mixture of the cyclopentadiene derivatives **3** and **22** in [$^2H_6$]benzene at 60 °C afforded a compound supposed to be

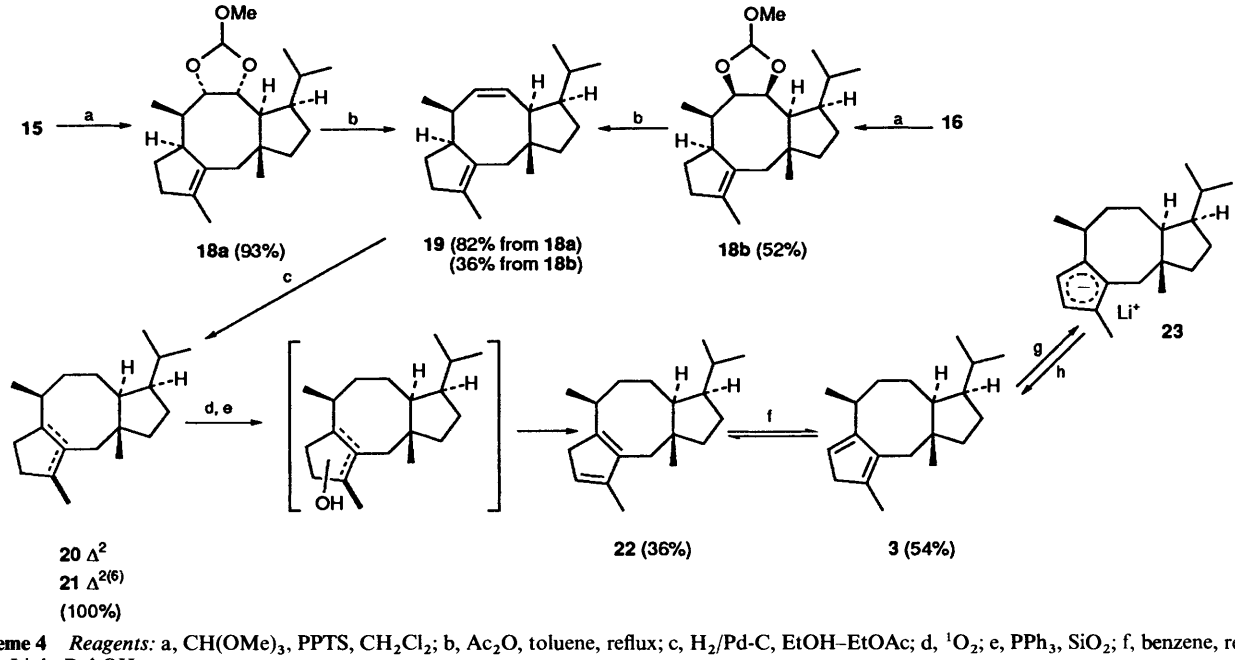
* The $TiCl_2$-mediated ring-closure in THF resulted in the formation of a seven-membered glycol **17** derived from an aldol condensate, in 39% yield. The yield of the desired product **15** was only 19%.

† Cyclopentadienes **3** and **22** caused an acid-induced rearrangement to a transoid diene, $\Delta^{2,6(7)}$-fusicoccadiene.

‡ Units of [α] are 10^{-1} deg cm^2 g^{-1}.



Scheme 3 *Reagents:* a, $CrCl_3$–LAH, DMF–THF–Pr^iOH; b, $CHMe_2CMe_2BH_2$, H_2O_2, OH^-; c, H_2/Pd-C; d, HCl–THF; e, Li, $EtNH_2$; f, $(COCl)_2$, DMSO, Et_3N; g, $TiCl_4$–Zn



Scheme 4 *Reagents:* a, $CH(OMe)_3$, PPTS, CH_2Cl_2; b, Ac_2O, toluene, reflux; c, H_2/Pd-C, EtOH–EtOAc; d, $^1O_2$; e, PPh_3, SiO_2; f, benzene, reflux; g, BuLi; h, Bu^t-OH

plagiospirolide **1**, as needles, m.p. 197–198 °C (lit.,[2] 197 °C) as the main product. Although the ^1H and ^{13}C NMR spectra of the synthetic sample revealed a small discrepancy with the reported data for the natural product **1**, the X-ray structural analysis of our compound revealed * the structure proposed for the natural product **1**.

We decided that it would be interesting to carry out a calculation study to analyse the preferential formation of the natural products. Although Fotiadu *et al.* have carried out a study which showed a preferential formation of the *exo*-adduct from simple Diels–Alder substrates, cyclopentadiene and α-methylene-γ-butyrolactone,[24] it is not enough solely to understand the exclusive formation of the natural products and the higher reactivity of diene **3** than that of its isomer **22**.

At first, semi-empirical molecular orbital calculations (MNDO/PM3)[25] were extended to a model system, that between 1,2,3-trimethylcyclopentadiene and α-methylene-γ-butyrolactone. There are four possible reaction modes, which are differentiated by the terms, *endo/exo* for the stereochemical selectivity and *favoured/disfavoured* for the regioselectivity according to molecular orbital considerations. The heats of formation of the four possible transition states were calculated as follows: $\Delta H_f = -49.33$ kcal mol^{-1} † for *exo-favoured* mode, $\Delta H_f = -44.75$ kcal mol^{-1} for *endo-favoured* mode, $\Delta H_f = -32.50$ kcal mol^{-1} for *exo-disfavoured* mode, and $\Delta H_f = -31.37$ kcal mol^{-1} for *endo-disfavoured* mode. Thus, compared with the other three, the value of the heat of formation for *exo-favoured* mode is small enough to conclude that this mode is actually the exclusive reaction pathway. Calculated stereo-

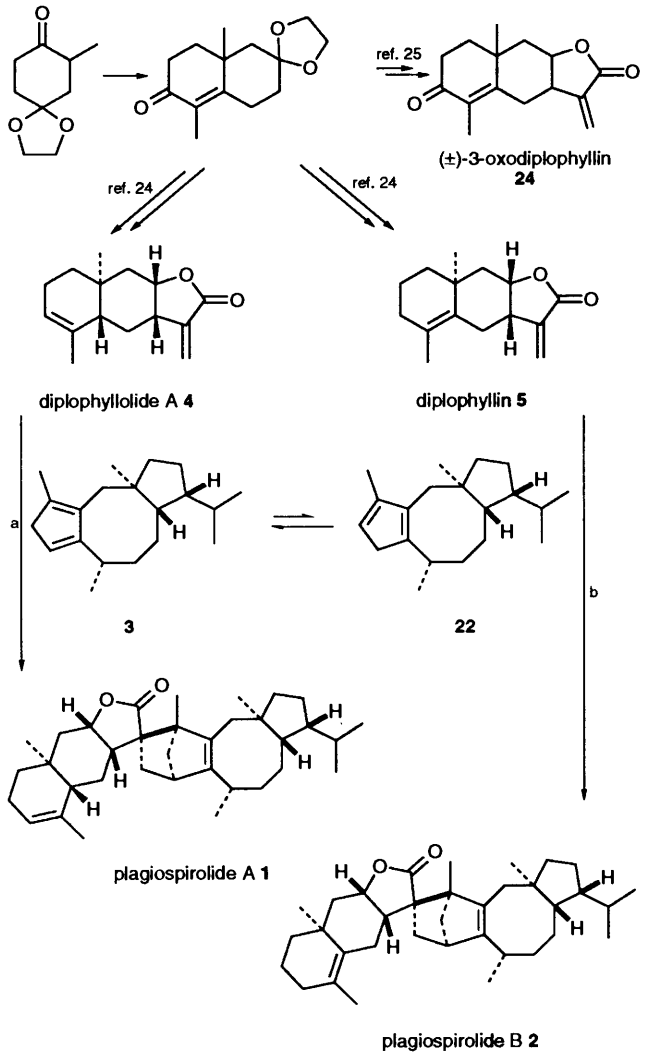
* X-Ray crystallographic analysis of compound **1** was reported in our preliminary paper, and the data were submitted to the Cambridge Crystallography Data Centre.

† 1 cal = 4.184 J.

structures for the four reaction modes (transition states) are shown in Fig. 3.

Then *exo-favoured* combinations of dienes **3** and **22** with lactone **4**, two for each combination, were evaluated by molecular mechanistic calculations (CAChe MM)* in which the geometries of the reaction sites were fixed as obtained from the above mentioned model studies. Since two of the four modes using a *concave* face of the dienophile **4** clearly have higher energies (ΔE_{st} = +13.3 kcal mol^{-1} for *concave*-**3** and ΔE_{st} = +10.2 kcal mol^{-1} for *concave*-**22** because of the severe steric interactions between the two components, the results only for the convex mode are shown in Fig. 4. Among these two modes, that of *convex*-**22** is unfavourable (ΔE_{st} = +3.9 kcal mol^{-1}) compared with that of *convex*-**3**, probably due to the following two reasons: (a) while *convex*-**3** possesses a relatively flat eight-membered ring which is similar to the conformation of plagiopiolide A **1** actually deduced from X-ray analysis and is the least energetic conformation in this system, the eight-membered ring of *convex*-**22** is forced to have a bent conformation; (b) since the secondary methyl group on the eight-membered ring is β-oriented (Fig. 4), it has a repulsive steric interaction with the dienophile **4** when the latter approaches from the β face of the diene as seen in the case of *convex*-**22**. Thus these computational studies support the observed preferential formation of the natural products and the inertness of diene **22** toward the Diels–Alder reaction with dienophiles **4** and **5**.

In conclusion, this work constitutes the first total synthesis of not only of the plagiospirolides **1** and **2** in optically active form, but also of the compound **3**, yet to be identified as a natural product. The fact that the Diels–Alder reaction of diene **3** with lactone **4** or **5** proceeded stereo- and substrate-selectively under nearly physiological conditions suggests that the natural products **1** and **2** could be formed non-enzymatically in the oily bodies of the liverwort.



Scheme 5 *Reagents and conditions:* a, benzene, reflux (60 °C); b, benzene, heat (25–60 °C)

Experimental

Elemental analyses were carried out by Mrs. M. Miyazawa and Mrs. Y. Hatazoe of the Institute of Advanced Material Study, Kyushu University. M.p.s were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. The NMR spectra were measured by means of JEOL FX 100 Model and GSX 270H Model spectrometers for solutions in $CDCl_3$, unless otherwise stated; chemical shifts are expressed in δ-units, and *J*-values are in Hz. Mass spectra were measured with a JEOL 01SG-2 spectrometer. IR spectra were taken as KBr disks for crystalline compounds or as liquid films inserted between NaCl plates for oily compounds, using a JASCO IR-A102 spectrometer. Optical rotations were measured with a Union Model PM-101 apparatus. The stationary phase for column chromatography was Wakogel C-300 and the eluent was an appropriate mixture of hexane and EtOAc.

Condensation of (3S,8R)-9-*Benzyloxyirid*-1-*en*-7-*al* **6** *and* (3R)-7-*Chloroirid*-1-*ene* **7**. *Formation of the Alcohol* **8**.—A suspension of $CrCl_3$ (17.16 g) in anhydrous THF (150 cm^3) was reduced with $LiAlH_4$ (LAH) (2.06 g) at 0 °C under argon. After being stirred for 1 h at room temperature, the resultant black suspension was diluted with DMF (300 cm^3) and then to the mixture were added, consecutively, Me_2CHOH (0.6 cm^3) and

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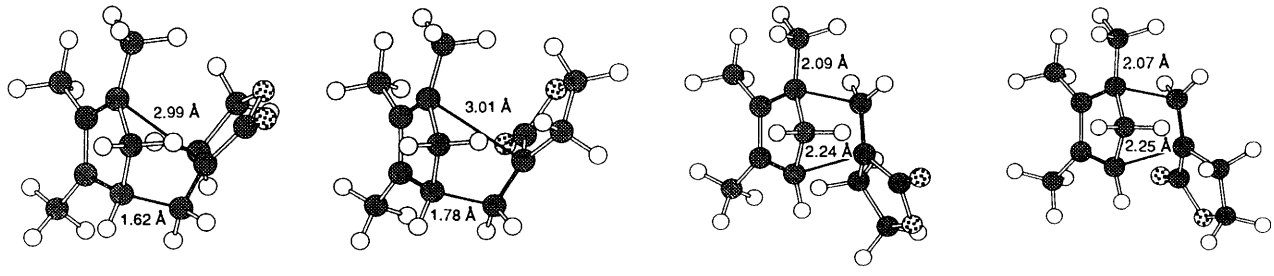
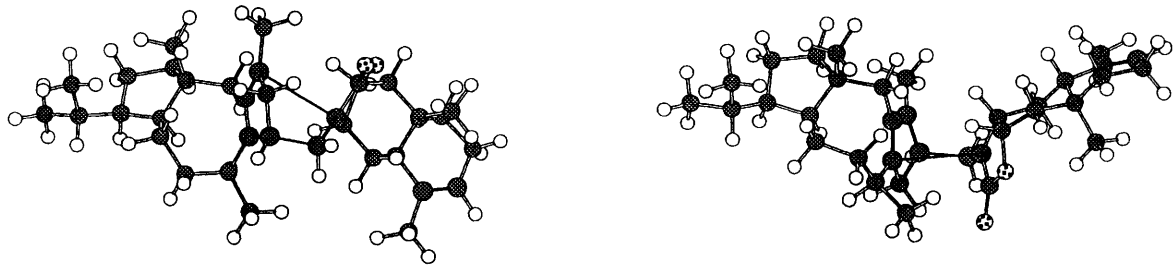


exo-favoured −49.33 kcal mol^{-1} | *endo-favoured* −44.75 kcal mol^{-1} | *exo-disfavoured* −32.50 kcal mol^{-1} | *endo-disfavoured* −31.37 kcal mol^{-1}

Fig. 3 Structures and heat of formations of the transition states calculated by MNDO/PM3 for the Diels–Alder reaction between 1,2,3-trimethylcyclopentadiene and α-methylene-γ-butyrolactone



(*convex*-face of lactone **4** to α-face of diene **3**)
ΔE_{st} = 0.00 kcal mol^{-1}

(*convex*-face of lactone **4** to β-face of diene **22**)
ΔE_{st} = +3.91 kcal mol^{-1}

Fig. 4 Relative steric energies of *exo-favoured-convex* modes between lactone **4** with dienes **3** and **22**

an anhydrous DMF solution (20 cm^3) of aldehyde **6** (11.2 g) and chloride **7** (9 g). After being stirred for 25 h at room temperature, the mixture was treated with water and extracted with hexane–EtOAc (5:1). The organic extract was washed with saturated aq. NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column to afford *compound* **8** as an oil (15.5 g, 90%) (Found: C, 81.8; H, 10.1. $C_{27}H_{38}O_2$ requires C, 81.77; H, 10.17%); $[\alpha]_D^{24}$ +43.3 (*c* 1.20, $CHCl_3$); δ_H 0.75 (3 H, d, *J* 7), 0.93 (3 H, d, *J* 7), 0.95 (3 H, d, *J* 7), 1.08 (3 H, s), 1.83 (3 H, br s), 2.57 (1 H, br s), 3.16 (1 H, dd, *J* 9 and 7), 3.55 (1 H, dd, *J* 9 and 5.5), 4.12 (1 H, br s), 4.40 (2 H, s), 4.81 (1 H, d, *J* 2), 5.00 (1 H, d, *J* 2) and 7.24 (5 H, br s); δ_C 16.5, 17.0, 17.2, 22.1, 23.4 (2 C), 23.6, 29.0, 34.4, 35.2, 39.1, 52.6, 54.3, 72.7, 73.3, 75.0, 105.5, 127.5, 127.7 (2 C), 128.3 (2 C), 136.8, 137.0, 138.5 and 161.2; *m/z* 259 (M^+ − 137) and 91 (base peak); ν_{max}/cm^{-1} 3590, 3470, 2960, 2870, 1642, 1499, 1455, 1367, 1096, 1029 and 733; and its *diastereoisomer* **9** as an oil (1.05 g, 6%) (Found: C, 81.5; H, 10.1%); δ_H 0.79 (3 H, d, *J* 7), 0.79 (3 H, s), 0.84 (3 H, d, *J* 7), 0.98 (3 H, d, *J* 7), 1.72 (3 H, br s), 2.82 (1 H, br s), 3.21 (1 H, dd, *J* 9 and 4.5), 3.35 (1 H, dd, *J* 9 and 8.5), 3.84 (1 H, br s), 4.32 (1 H, d, *J* 12), 4.44 (1 H, d, *J* 12), 4.66 (1 H, br s), 4.83 (1 H, d, *J* 3), 4.99 (1 H, d, *J* 3) and 7.24 (5 H, br s); δ_C 14.9, 16.2, 17.8, 21.7, 22.1, 23.5, 25.6, 27.7, 32.3, 35.6, 37.5, 51.1, 51.3, 52.0, 71.7, 73.3, 75.4, 103.1, 127.5, 127.7 (2 C), 128.2 (2 C), 136.8 (2 C), 137.8 and 162.2; *m/z* 259 (M^+ − 137) and 91 (base peak); ν_{max}/cm^{-1} 3460, 2960, 1645, 1456, 1370, 1205, 1100, 1080, 1030, 1000, 878 and 738 cm^{-1}.

Conversion of Compound **8** *into Triol* **11** via *Diol* **10** *by Hydroboration and Hydrogenolysis*.—A THF solution (30 cm^3) of compound **8** (4.8 g) was added to a THF solution (150 cm^3) of thexylborane which was prepared from 2,2-dimethylbut-2-ene (7.2 cm^3), BF_3·Et_2O (7.4 cm^3) and $NaBH_4$ (2.75 g), at 0 °C and the mixture was stirred at room temperature for 15 h. The mixture was then treated with 3 mol dm^{-3} NaOH (20 cm^3) and H_2O_2 (35%; 15 cm^3) to give, after work-up and chromatographic purification, diol **10** as needles, m.p. 89.5–91.5 °C (4.4 g, 88%); $[\alpha]_D^{24}$ −22.7 (*c* 1.63, $CHCl_3$); δ_H 0.81 (3 H, d, *J* 7), 0.93 (3 H, d, *J* 7), 0.99 (3 H, s), 1.27 (3 H, d, *J* 7), 1.81 (3 H, br s), 2.64 (1 H, br s), 3.20 (1 H, dd, *J* 9.5 and 7.5), 3.34 (1 H, dd, *J* 9.5 and 7.5), 3.46 (1 H, t, *J* 10.5), 3.68 (1 H, dd, *J* 10.5 and 3.5), 3.93 (1 H, br s), 4.31 (1 H, d, *J* 11.5), 4.43 (1 H, d, *J* 11.5) and 7.27 (5 H, m); δ_C 16.4, 17.0, 17.2, 21.4, 22.9, 23.7, 27.7 (2 C), 35.2, 38.4, 39.1, 50.2, 51.1, 51.8, 53.8, 59.8, 73.0, 73.5, 78.5, 127.8 (3 C), 128.4 (2 C), 136.7, 137.0 and 138.0; *m/z* 414 (M^+) and 91 (base peak); ν_{max}/cm^{-1} 3260, 2970, 2900, 2860, 1498, 1453, 1370, 1100, 1075, 1030, 1020 and 743.

Subsequently, an EtOH solution (20 cm^3) of diol **10** (5.0 g) was hydrogenated with Pd/C (500 mg) at room temperature. After the catalyst had been filtered off, the solution was evaporated under reduced pressure and the resultant residue was purified *via* silica gel column chromatography to give *triol* **11** as scales, m.p. 159.5–160.5 °C (2.93 g, 75%) (Found: C, 74.15; H, 11.3. $C_{20}H_{36}O_3$ requires C, 74.03; H, 11.18%); δ_H 0.83 (3 H, d, *J* 7), 0.94 (3 H, d, *J* 7), 0.96 (3 H, s), 0.98 (3 H, d, *J* 7), 1.87 (3 H, br s), 2.62 (1 H, m), 3.28 (1 H, dd, *J* 10.5 and 6), 3.51 (1 H, dd, *J* 11 and 10.5), 3.51 (1 H, dd, *J* 10.5 and 6), 3.76 (1 H, dd, *J* 11 and 3.5) and 4.01 (1 H, br s); δ_C 16.2, 17.0, 17.1, 21.4, 22.8, 23.8, 27.5, 27.7, 37.8, 38.4, 39.3, 50.0, 51.4, 52.3 (2 C), 54.0, 59.8, 64.4, 136.7 and 137.6; ν_{max}/cm^{-1} 3220, 2970, 2880, 1454, 1370, 1365 and 1038; and the *cyclic ether* **12** as an oil (782 mg, 20%) (Found: C, 78.2; H, 11.0; $C_{20}H_{34}O_2$ requires C, 78.38; H, 11.18%); $[\alpha]_D^{28}$ +57.4 (*c* 1.62, $CHCl_3$); δ_H 0.78 (3 H, d, *J* 6.6), 0.88 (3 H, d, *J* 6.6), 0.93 (3 H, d, *J* 6.3), 1.27 (3 H, s), 1.28 (3 H, s), 2.12 (1 H, sept. d, *J* 6.6 and 2), 2.97 (1 H, br d, *J* 4.4), 3.36 (1 H, t, *J* 11.5), 3.66 (1 H, dd, *J* 11.5 and 6.5), 3.78 (1 H, dd, *J* 11.5 and 3) and 5.28 (1 H, s); δ_C 14.9, 20.9, 21.2, 22.2, 22.4, 24.5, 28.3, 29.9, 33.8, 37.0, 39.1, 43.2, 46.1, 50.2, 54.1, 60.4, 66.9, 80.4, 128.3 and 147.4; *m/z* 306 (M^+) and 151 (base peak); ν_{max}/cm^{-1} 3450, 2950, 2860, 1470, 1468, 1385, 1320, 1095, 1060 and 985.

Acid-induced Ether Formation of Compound **12** *from Triol* **11**.—An EtOH solution (2 cm^3) of triol **11** (1.0 g) and conc. HCl (0.05 cm^3) was stirred at room temperature for 2 h. The mixture was then diluted with water, extracted with diethyl ether, and the extract consecutively washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl, and dried over $MgSO_4$. The residue obtained by removal of the solvent under reduced pressure was chromatographed on a silica gel column to give the ether **12** (755 mg, 80%).

Birch Reduction of Cyclic Ether **12** *to Diol* **13**.—To a THF solution (50 cm^3) of $EtNH_2$ (200 cm^3) added was Li (360 mg) under N_2 at −78 °C to obtain a blue solution. A THF solution (10 cm^3) of compound **12** (3.2 g) was added drop by drop and the mixture was stirred for a further 2 h. The mixture was then treated with $PhCO_2Na$ to neutralize an excess of Li, diluted with aq. NH_4Cl, extracted with diethyl ether, washed successively with saturated aq. NaCl and water, and dried over $MgSO_4$. The residue obtained by removal of the solvent was chromatographed on a silica gel column to give *diol* **13** as an oil (2.2 g, 68%) (Found: C, 77.7; H, 11.8. $C_{20}H_{36}O_2$ requires C, 77.86; H, 11.76%); δ_H 0.90 (3 H, d, *J* 6.2), 0.93 (3 H, d, *J* 6.6), 0.95 (3 H, d, *J* 7), 1.09 (3 H, s), 1.62 (3 H, d, *J* 1), 1.5–1.7 (4 H, m), 1.7–1.95 (3 H, m), 2.15 (1 H, d, *J* 14), 2.18–2.28 (2 H, m), 2.31 (1 H, d, *J* 14), 2.83 (1 H, br d, *J* 7.7), 3.28 (1 H, dd, *J* 10.6 and 7.7), 3.52 (1 H, dd, *J* 10.6 and 5.5), 3.66 (1 H, dd, *J* 11.4 and 6.2) and 3.76 (1 H, dd, *J* 11.4 and 3.6); δ_C 15.2, 16.5, 22.2, 22.6 (2 C), 23.8, 28.6, 29.4, 36.5, 37.3, 38.8, 39.4, 46.7, 49.3, 50.3, 52.3, 60.9, 65.7 and 136.0 (2 C); *m/z* 308 (M^+) and 95 (base peak); ν_{max}/cm^{-1} 3300, 2880, 1465, 1430, 1360, 1350, 1200, 1010 and 960.

Swern Oxidation of Diol **13** *to Dial* **14**.—A CH_2Cl_2 solution (20 cm^3) of dimethyl sulfoxide (DMSO) (1.66 cm^3) was added during 30 min at −78 °C to a CH_2Cl_2 solution (3.0 cm^3) of $(COCl)_2$ (1.0 cm^3) and the mixture was stirred at this

temperature for 15 min under N_2. A THF solution (10 cm^3) of diol **13** (1.20 g) was then added and the mixture was stirred for a further 1 h; after the addition of Et_3N (10.8 cm^3), the temperature was gradually raised to −10 °C, and the mixture was treated with aq. $NaHCO_3$. The mixture was then extracted with hexane–EtOAc (5:1) and the extract was dried over $MgSO_4$, the solvent was evaporated off and the residue was chromatographed on a silica gel column to give *dial* **14** as an oil (887 mg, 74%) (Found: M^+, 304.2402. $C_{20}H_{32}O_2$ requires M, 304.2402); $[\alpha]_D^{17}$ −48.15 (*c* 1.35, $CHCl_3$); δ_H 0.84 (3 H, d, *J* 6.6), 0.93 (3 H, d, *J* 6.2), 1.02 (3 H, s), 1.05 (3 H, d, *J* 7), 1.64 (3 H, d, *J* 1.1), 2.41 (1 H, t, *J* 6.5), 2.41 (1 H, d, *J* 13.5), 2.71 (1 H, tddd, *J* 7, 3.7, 3.3 and 1.5), 3.02 (1 H, br s), 9.64 (1 H, d, *J* 1.5) and 9.74 (1 H, d, *J* 6.6); δ_C 12.0, 14.0, 15.1, 21.5, 22.3, 24.1, 24.6, 29.3, 30.0, 36.9, 38.4, 39.4, 48.0, 50.4, 51.5, 62.4, 132.5, 138.5, 205.8 and 205.9; *m/z* 304 (M^+) and 95 (base peak); ν_{max}/cm^{-1} 2970, 2860, 1715, 1450, 1380, 1220 and 1055.

Titanium(II) *Chloride-mediated Coupling of Dial* **14** *to give Glycols* **15** *and* **16** *in a Mixture of THF and Benzene*.—To a stirred mixed solution (200 cm^3) of anhydrous THF and benzene (1:5) of $TiCl_4$ (7.2 cm^3) was added Zn (8.63 g) at 0 °C under N_2. After being stirred for 3 h at room temperature, the mixture was treated with pyridine (5.3 cm^3), to which dial **14** (860 mg) in a mixed solution (20 cm^3) of THF and benzene (1:5) was introduced by means of a Microfeeder within a 50 h period. After being stirred for a further 5 h, the mixture was diluted with aq. K_2CO_3, extracted with hexane–EtOAc (3:1), and the extract washed with aq. $KHSO_4$ and saturated aq. NaCl, and dried over $MgSO_4$. The residue obtained by removal of the solvent under reduced pressure was chromatographed on a silica gel column to give cis-*glycol* **15** as crystals, m.p. 74.5–76 °C (320 mg, 37%) (Found: C, 78.2; H, 11.2. $C_{20}H_{34}O_2$ requires C, 78.38; H, 11.18%); $[\alpha]_D^{29}$ +50.5 (*c* 1.23, $CHCl_3$); δ_H 0.81 (3 H, s), 0.91 (3 H, d, *J* 6.7), 0.93 (3 H, d, *J* 6.7), 0.96 (3 H, d, *J* 7), 1.2–1.5 (6 H, m), 1.61 (3 H, s), 1.62 (1 H, br d, *J* 13.9), 1.85–1.94 (3 H, m), 2.02 (1 H, br s), 2.21 (1 H, m), 2.22 (1 H, br d, *J* 9.5), 2.31 (1 H, qd, *J* 7 and 3.5), 2.42 (1 H, m), 2.48 (1 H, d, *J* 13.9), 2.65 (1 H, m), 3.57 (1 H, br s) and 3.79 (1 H, br d, 9.9); δ_C 14.7, 15.2, 19.3, 20.3, 21.5, 24.3_7, 24.3_9, 26.2, 31.6, 36.9, 41.7, 44.6, 45.6, 47.1, 55.0, 55.3, 70.3, 74.9, 135.3 and 136.9; *m/z* 306 (M^+) and 151 (base peak); ν_{max}/cm^{-1} 3428, 2924, 1627, 1459, 1390, 1037 and 970; and its diastereoisomer **16** as crystals, m.p. 69–70 °C (78 mg, 9%) (Found: C, 78.2; H, 11.2%); $[\alpha]_D^{29}$ + 29.9 (*c* 1.19, $CHCl_3$); δ_H 0.90 (3 H, d, *J* 6.8), 0.92 (3 H, d, *J* 6.8), 1.09 (3 H, s), 1.22 (3 H, d, *J* 7), 1.40 (1 H, td, *J* 12 and 7), 1.47 (1 H, dd, *J* 12 and 6.5), 1.57 (1 H, dtd, *J* 13, 7.5 and 2.4), 1.64 (1 H, dt, *J* 13 and 7.7), 1.71 (3 H, s), 1.72 (1 H, d, *J* 13), 1.86 (1 H, dd, *J* 11.4 and 1.5), 1.93 (1 H, d, *J* 13), 1.94 (1 H, td, *J* 9.3 and 6.5), 2.02 (1 H, dt, *J* 12.7 and 7.7), 2.07–2.2 (2 H, m), 2.29 (1 H, dd, *J* 15.8 and 9.3), 2.33 (1 H, qt, *J* 6.8 and 3.6), 2.48 (1 H, d, *J* 13), 2.55 (1 H, d, *J* 8.4), 2.59 (1 H, br s), 3.43 (1 H, ddd, *J* 8.4, 5 and 3.5 Hz) and 4.14 (1 H, ddd, *J* 13, 5 and 1.5); δ_C 16.2, 18.1, 18.8, 23.1 (2 C), 23.8, 25.6, 28.1, 33.9, 36.6, 40.1, 44.6, 46.3, 48.1, 49.1, 54.7, 72.0, 77.9, 137.9 and 140.2; *m/z* 306 (M^+) and 95 (base peak); ν_{max}/cm^{-1} 3450, 2925, 1630, 1460, 1370, 1040 and 970.

Reductive Elimination of the Oxygen Functionality of Diol **15** *to give Diene* **19** via *Orthoformate* **18a**.—A CH_2Cl_2 solution (5 cm^3) of diol **15** (320 mg), $CH(OMe)_3$ (5 cm^3) and pyridinium toluene-*p*-sulfonate (PPTS) (50 mg) was stirred at room temperature for 5 h under N_2. The mixture was then diluted with aq. $NaHCO_3$ and extracted with hexane–EtOAc (10:1). After evaporation of the organic extract under reduced pressure, the resultant residue was worked up similarly and purified *via* a silica gel column chromatography to give orthoformate **18a** as an oil (340 mg, 93%); δ_H 0.79 (3 H, s), 0.88 (3 H, d, *J* 7), 0.91 (3 H, d, *J* 6.6), 0.95 (3 H, d, *J* 6.6), 1.58 (3 H, s), 2.67 (1 H, m), 3.33 (3 H, s), 3.99 (1 H, dd, *J* 6.6 and 4.8), 4.23 (1 H, dd, *J* 10.7 and 4.8) and 5.64 (1 H, s); δ_H 15.4, 15.8, 19.2, 20.9, 22.6, 22.9, 24.6, 26.2, 30.3, 36.8, 41.6, 44.5, 44.7, 48.5, 49.6, 52.0, 54.5, 76.5, 76.7, 114.8, 133.8 and 137.3.

Then, the resultant orthoformate **18a** (340 mg) was dissolved in toluene (1.7 cm^3)–Ac_2O (3.3 cm^3) and the mixture was refluxed for 3 h. The mixture was poured into ice–aq. K_2CO_3 and extracted with hexane. The extract was then dried over $MgSO_4$ and evaporated to remove the solvent. Silica gel column chromatography of the residue afforded *diene* **19** as an oil (218 mg, 82%) (Found: M^+ 272.2527. $C_{20}H_{32}$ requires M, 272.2502); $[\alpha]_D^{18}$ +18.6 (*c* 1.45, $CHCl_3$); δ_H 0.70 (3 H, s), 0.87 (3 H, d, *J* 6.6), 0.88 (3 H, d, *J* 6.2), 1.01 (3 H, d, *J* 6.6), 1.55 (3 H, d, *J* 3.3), 2.08–2.18 (2 H, m), 2.44 (1 H, d, *J* 13.6), 2.78 (1 H, m), 2.86 (1 H, t, *J* 10), 2.98 (1 H, tt, *J* 10 and 7), 5.32 (1 H, td, *J* 10 and 1.5) and 5.55 (1 H, br t, *J* 10); δ_C 15.6, 19.1, 20.0, 21.1, 23.3, 24.0, 28.7, 30.1, 32.2, 36.6, 41.1, 42.5, 48.2, 48.7, 49.7, 60.1, 130.7, 133.2, 135.4 and 136.1; *m/z* 272 (M^+) and 229 (base peak); ν_{max}/cm^{-1} 3050, 1480, 1410, 830 and 790.

Reductive Elimination of the Oxygen Functionality of Glycol **16** *to give Diene* **19** via *Orthoformate* **18b**.—Similarly, the orthoformate **18b** was obtained as needles, m.p. 100–103 °C (90 mg, 52%); δ_H 0.93_8 (3 H, d, *J* 6.6), 0.94_2 (3 H, d, *J* 6.6), 1.02 (3 H, s), 1.20 (3 H, d, *J* 7.3), 1.60 (3 H, br d), 2.48 (1 H, d, *J* 13.2), 2.68 (1 H, br m), 3.25 (3 H, s), 4.25 (1 H, d, *J* 8.1), 4.63 (1 H, d, *J* 8.1), 4.63 (1 H, td, *J* 8.1) and 5.46 (1 H, br s); δ_C 15.8, 18.0, 21.1, 22.7, 23.4_0, 23.4_2, 23.7, 28.1, 32.8, 36.9, 41.6, 45.1, 46.5, 47.0, 48.5, 51.7, 54.3, 75.3, 83.9, 114.1, 134.1 and 134.6.

Orthoformate **18b** (31 mg) then gave the diene **19** (8 mg, 36%).

Catalytic Reduction of Diene **19** *to Alkenes* **20** *and* **21**.—An EtOH solution (4 cm^3) of diene **19** (120 mg) containing Pd/C (12 mg) and EtOAc (0.5 cm^3) was stirred under hydrogen for 15 h. Then the mixture was passed through a Celite column to remove the catalyst, and the filtrate was diluted with water and extracted with hexane. Silica gel column chromatography of the extract afforded a 5:3 mixture (122 mg, quantitative) of alkene **20**; δ_H 0.80 (3 H, d, *J* 7), 0.81 (3 H, s), 0.87 (3 H, d, *J* 7), 0.91 (3 H, d, *J* 7) and 1.60 (3 H, br s); and its regioisomer **21**; δ_H 0.73 (3 H, s), 0.79 (3 H, d, *J* 7), 0.88 (3 H, d, *J* 7), 0.99 (3 H, d, *J* 7) and 1.00 (3 H, d, *J* 7).

Oxidation of Alkenes **20** *and* **21** *with* $^1O_2$: *Formation of a Mixture of Cyclopentadienes* **3** *and* **22**.—An acetone solution (10 cm^3) of a mixture of alkenes **20** and **21** (210 mg), pyridine (0.1 cm^3), and Rose Bengal (1 mg) was exposed to visible light (400 W tungsten lamp) under a stream of oxygen for 20 min. The mixture was treated with Ph_3P and heated under reduced pressure to evaporate volatile material. The residue was adsorbed on a silica gel plate and left at room temperature for 3 h. Then, after development with hexane–EtOAc (5:1), the least polar portion was washed with EtOAc to give an oily mixture (190 mg, 91%) of diene **3**, $\delta_H(C_6D_6)$ 0.74 (3 H, s), 0.74 (3 H, d, *J* 7), 0.89 (3 H, d, *J* 7), 1.27 (3 H, d, *J* 7), 1.86 (3 H, br s) and 5.89 (1 H, br s) and diene **22**, $\delta_H(C_6D_6)$ 0.73 (3 H, d, *J* 7), 0.74 (3 H, s), 0.90 (3 H, d, *J* 7), 1.10 (3 H, d, *J* 7), 1.94 (3 H, q, *J* 2) and 5.94 (1 H, sext, *J* 2).

Selective Formation of Diene **3** via BuLi-*Treatment of a Mixture of Isomers* **3** *and* **22**.—An anhydrous THF solution (2 cm^3) of dienes **3** and **22** (15 mg; 3:2) was treated with a hexane solution (0.11 cm^3) of BuLi (0.275 mmol) at −78 °C to form a cyclopentadienide **23** and the mixture was gradually warmed to −20 °C. The mixture was, while being continuously stirred, treated with Bu^tOH and then diluted with saturated aq. $NaHCO_3$ and extracted with hexane. ^1H NMR spectroscopy indicated the extract contained only diene **3**.

Thermal Equilibrium of Dienes **3** *and* **22**.—A benzene solution of diene **3** was heated at 80 °C for 1 h. ^{1}H NMR spectrometry revealed the ratio of isomeric dienes **3** and **22** was 3:2.

Diels–Alder Reaction of Compounds **3** *and* **5**.—(*a*) A [$^2H_6$]benzene solution (0.3 cm^3) of a mixture of dienes **3** and **22** (7 mg) and lactone **5** (6 mg) was placed in an NMR tube and kept at room temperature (25 °C) for 5 h. ^{1}H NMR spectrometry indicated, in respect of disappearance of the exocyclic methylene signals of the isomeric lactone that reaction had proceeded to the extent of ~ 15%.

(*b*) The above [$^2H_6$]benzene solution (0.3 cm^3) obtained starting from a mixture of dienes **3** and **22** (7 mg) and lactone **4** (6 mg) was, without work-up, heated at 40 °C for 12 h (35% conversion) and then at 60 °C for 28 h (65% conversion) with occasional monitoring of the reaction. The mixture was then heated under reduced pressure to remove the solvent, and silica gel column chromatography of the residue afforded plagiospirotide **B 2** as an oil (5 mg, 68% based on conversion); δ_H 0.74 (3 H, d, *J* 7), 0.74 (3 H, s), 0.87 (3 H, d, *J* 6.5), 1.05 (3 H, s), 1.10 (3 H, d, *J* 7), 1.26 (3 H, s), 1.56 (3 H, br s), 2.06 (1 H, dd, *J* 11 and 6.5), 2.17 (1 H, dd, *J* 12 and 3.5), 2.68 (1 H, sept, *J* 6.5), 2.87 (1 H, br d, *J* 3) and 4.48 (1 H, td, *J* 7.5 and 4.5); δ_C 14.8, 18.6, 18.7, 18.9, 19.1, 20.7, 21.4, 23.4, 23.9, 26.2, 26.9, 28.4, 30.2, 32.1, 33.4, 36.8, 37.6, 37.7, 40.1, 40.4, 41.6, 42.8, 43.1, 46.0, 47.2, 48.0, 51.3, 58.5, 61.6, 76.2, 126.3, 132.5, 140.4, 149.7 and 182.8.

Diels–Alder Reaction of Compounds **3** *and* **4**.—Similarly, a [$^2H_6$]benzene solution (0.3 cm^3) of compound **3**, as a mixture with its isomer **22** (15 mg) and lactone **4** (7 mg) was placed in an NMR tube and kept at 60 °C from the initial stage, and the reaction was allowed to continue for 90 h (> 95% conversion) with occasional monitoring. The mixture was then heated under reduced pressure to remove the solvent, and silica gel column chromatography of the residue afforded plagiospirolide **A 1** as crystals, m.p. 197–198 °C (12 mg, 79%); δ_H 0.74 (3 H, d, *J* 7), 0.74 (3 H, s), 0.83 (3 H, s), 0.87 (3 H, d, *J* 6.5), 1.08 (3 H, d, *J* 7), 1.33 (3 H, s), 1.58 (3 H, br s), 2.22 (1 H, dd, *J* 12 and 3.5), 2.72 (1 H, sept, *J* 6.5), 2.82 (1 H, br d, *J* 3), 4.67 (1 H, td, *J* 4.5 and 1) and 5.34 (1 H, br m); δ_C 16.4 (q), 17.2 (q), 18.7 (q), 18.9 (q), 20.7 (t), 21.0 (q), 21.4 (q), 22.2 (t), 23.4 (q), 24.0 (t), 25.8 (t), 28.4 (d), 30.1 (d), 30.7 (s), 36.6 (t), 36.8 (t), 37.9 (t), 39.8 (d), 40.0 (t), 41.6 (2 C, t), 43.7 (d), 44.3 (d), 46.0 (s), 47.2 (d), 48.0 (d), 52.1 (t), 61.6$_1$ (s), 61.6$_4$ (s), 76.8 (d), 122.2 (d), 133.4 (s), 140.1 (s), 150.2 (s) and 182.1 (s).

Computational Procedure.—The semi-empirical molecular orbital calculations were performed with MNDO/PM3 implemented in the MOPAC ver. 6.10 program included in the CAChe system (SONY-Tektronix). The structures of the transition states for the model system were optimized by 'TS' and 'PRECISE' options, and it was confirmed that all the transition structures obtained have only one imaginary frequency by vibrational-frequency-calculation analyses. Then the heats of formation were calculated for the optimized structures by including configuration interactions with 'C.I. = 2'. The CAChe extended MM2 program ver. 3.5 (CAChe Scientific Inc.) was used for the molecular mechanistic calculations of transition states of lactone **4** with dienes **3** and **22** using the 'Lock Atoms' option for the diene and dienophile portions. Numbers of conformers about the central eight-membered ring and the isopropyl group were calculated and the results shown in Fig. 4 are the least energetic ones for each case. Several other possible candidates, including '*endo-favoured-convex*' were also calculated similarly and were found not to be competitive with '*exo-favoured-convex*-**3**.'

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